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STUDIES ON THE EARLY TYPE OF FATTY LIVER DEVELOPED IMMEDIATELY AFTER TOTAL PANCREATECTOMY : ESPECIALLY ON THE AMOUNT OF INSULIN ADMINISTERED

by

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INTRODUCTION

In 1889 von MEHRING and MINKOWSKI reported that total pancteatectomy caused diabetes. In 1922 BANTING and BEST discovered insulin, and 1924 FISHER found out that it was impossible for a totally depancreatized dog to live long after the operation, even though treatment with insulin would be given to regulate diabetes, and he expressed the opinion that the cause of death might well be fatty liver. Later MACLEOD, HERSHEY, SOSKIN, BEST, and others studied how to prevent the development of fatty liver, and MACLEOD found in raw pancreas the function to check the occurrence of fatty liver, while HERSHEY and SOSKIN recognized the anti-fatty liver activity in "lecithin" of an egg-yolk. BEST, HERSHEY, HUNTMAN and others perceived that activity in coline, an ingredient of lecithin, which they named "lipotropic substance." In 1931, TUCKER and ECKSTEIN found that methionine had the lipotropic action, and explained that this action was due to nothing but the coline whose synthesis in the body was accelerated by methionine.

This series of studies was concerned only with cases which survived for a considerably long time after the operation, and not with the condition of livers immediately after the operation. Besides the above mentioned studies, in 1940, DRAGSTEDT reported in the conclusions of his experiments that a marked accumulation of fat was found in the liver of a totally depancreatized dog soon after the operation; and that though administration of an adequate amount of insulin could prolong the length of survival, restoring the condition of its liver almost to its previous state, yet the dog died 6 to 8 weeks later, due to the later type of fatty liver which developed, as he insisted, from the deficiency of a pancreatic hormone, "Lipocaic." He presumed that the fatty liver which developed immediately after total pancreatectomy was diabetic in origin, essentially different from what developed at a later stage, since the early type of fatty liver could be cured by a proper amount of insulin.

Furthemore, in 1935, CHAIKOFF and KAPLAN observed the fact that totally depancreatized dogs, which had been made alive under good nutritional conditions for 4 to 14 weeks after the operation, developed a fatty liver (20-40%) within a week after both insulin and diet were cut off. From this observation they pointed

out that the lack of insulin after total pancreatectomy caused the development of fatty liver in the later period.

Now, according to OHNO of Japan, in spite of continuous administration of insulin to totally depancreatized dogs, within 24 hours after the operation their liver cells showed fat globules which so increased in the course of time that liver lobules appeared completely fatty. He adds, however, that administration of methionine and vitamin B_{12} causes only a very small number of fat globules to appear in the liver cells 5 days after the operation, and that those very small amounts of fat are likely to disappear gradually in the course of time. He emphasizes that fatty liver which develops after total pancreatectomy should not be divided into two types — the early and later types, but it could be recognized any time after the operation and be treated by methionine and vitamin B_{12}.

As is understood from the above, studies on fatty liver which develops after total pancreatectomy show different results and pose difficult problems which have not yet been completely solved.

Studies pursued in our clinic have made it clear that fatty liver developed soon after total pancreatectomy disappears in about 2 weeks after the operation if insulin is administered continuously. Experiments by AOKI showed that three totally depancreatized dogs which received no insulin died 4 to 6 days after the operation, and that a marked accumulation of fat was recognized in their livers. From these I have come to conclude that the fatty liver developed soon after the operation is due to diabetes caused by the lack of insulin. On the basis of this jndgment, I carried out experiments concerning the relation between insulin and fatty liver, taking into consideration also the effects of methionine and vitamin B_{12}.

EXPERIMENTAL PROCEDURE

1) Adult dogs weighing about 10kg were used.

2) For anesthesia 0.04 to 0.05g per kg body weight of isomytal or nembutal was injected intravenously.

3) The pancreas was removed completely and much attention was paid not to injure the pancreatico-duodenal artery as much as possible. After the operation, impairment of passage in the duodenum was observed in a few cases, but no case suffered from complete necrosis of the duodenal wall. At autopsy no case was found with the pancreatic tissue which had been left at the time of the operation.

4) The blood-sugar level was measured by the micro-method of SOMOGYI before and after the operation.

5) A piece of the liver tissue was removed by laparotomy, and the total amount of fatty acid was chemically determined by the VAN de KAMER method.

6) Fat in the liver was histologically tested by the method of SUDAN III stain, which was applied to carbowax sections.

All the totally pancreatectomized dogs were divided into the following five groups, and fat in their liver was examined until 2 weeks after the operation.

1) Group I includes cases in which no insulin was administered.

2) Group II includes cases where a small amount of insulin was administered.

3) Group III includes cases in which a small amount of insulin was administered together with both methionine and vitamin B_{12}.

4) Group IV includes cases in which a large amount of insulin was administered.

5) Group V includes cases in which a large amount of insulin was administered together with both methionine and vitamin B_{12}.

RESULTS OF EXPERIMENTS

The total amount of hepatic fatty acid in normal dogs

According to the experiments hitherto made, the liver of a normal dog contains 2 to 3g% of fatty acid. My experiments showed that no case contained more than 4g%, with 2.85g% on the average. Therefore, I have considered values less than 4g% as normal.

Table: 1 Group I (cases in which no insulin was administered.)

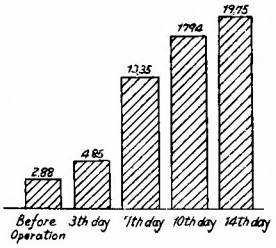
	Before Operation	Died	Amount of Fatty Acid
No. 19	2.21 g%	on 5th postoperative day	14.88 g%
No. 17	2.82 g%	on 4th postoperative day	7.08 g%
No. 20	2.05 g%	on 4th postoperative day	Fatty Liver Occurred
No. 23	2.61 g%	on 6th postoperative day	Fatty Liver Occurred
No. 32	3.00 g%	on 6th postoperative day	Fatty Liver Occurred

1) Group I

According to Aoki in our clinic, every totally depancreatized dog, which was given no insulin after the operation, died of a highly developed fatty liver. Five cases on which I experimented died within a week after the operation, having a marked accumulation of fat in its liver, so that it could easily be demonstrated macroscopically. As in Table I, two cases, in which the amount of fat was chemically determined, showed at autopsy a remarkable increase of fat in the liver, that is, 7.08g% for No. 17 and 14.88g% for No. 19. The blood-sugar level began to

Table 2: Changes in the total amount of fatty acid in cases of group II in which small amount of insulin was given. (g%)

	Before Operation	After Operation 3th day	7th day	10th day	14th day
No.35	3.14	4.48		17.77	
No.39	2.93	5.23		18.10	
No.37	2.63		18.51		22.66
No.41	2.44		10.20		17.44
No.87	3.23				16.60
No.91	2.86				22.31
No.95	2.77		10.41		
No.97	3.04		14.27		



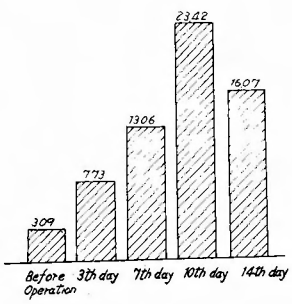
rise immediately after the operation and in 2 hours showed such high values as 180 mg% to 200mg%. The dogs in this group showed no appetite at all, and were weakened very much, compared with those given insulin. The histological findings of the liver cells of the two cases showed that they were full of fat globules, with their nuclei destroyed or missing, and with vacuoles formed showing a finding of "totale Verfettung" in German.

2) Group II

Since dogs receiving no insulin died within a week after the operation, I tried to lengthen the survival period of dogs belonging to group II by injecting a very small amount of insulin, that is, 0.3u. per kg body weight. As shown in Table 2, the result was that except those which died from the operation, every case could maintain their lives far longer than those of group I. However, the cases in this group, with no exceptions, could not escape from the development of fatty liver, and about 10 days after the operation they all showed a marked accumulation of fat in their livers — more than 10g% (Fig. 5). In other words, 0.3u. per kg body weight of insulin was not enough to prevent, on the one hand, a development of fatty liver soon after the operation, and, on the other, the high degree of asthenia, as was observed in group I. Nor could it prevent the amount of fat from increasing as days passed.

Table 3: Changes in the total amount of fatty acid in cases of group III in which were given both methionine, vitamin B_{12} and small amount of insulin. (g%)

	Before Operation	After Operation			
		3th day	7th day	10th day	14th day
No.48	3.02	5.06			
No.49	2.26			39.93	
No.55	3.42	10.46		14.07	
No.67	3.34	7.67		16.28	
No.43	3.23		16.20		
No.45	2.92				25.76
No.47	3.30		13.25		6.24
No.53	2.99		14.29		17.71
No.57	3.40		8.42		14.60



3) Group III

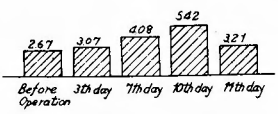
In order to test the effectiveness of methionine and vitamin B_{12}, methionine and vitamin B_{12}, as well as the small amount of insulin as was used in group II, were given to the cases of group III. 350 mg of methionine and 50γ of vitamin B_{12} per day was injected into them subcutaneously once a day. The result was that, although one case, No. 47, showed a decrease of fat in the liver from 13.25 g% (on the 7th postoperative day) to 6.24g% (on the 14th postoperative day), all the other cases showed a continuously increasing amount of fat in the liver in the course of time (Table 3). To take case No. 49, for example, the total amount of

fatty acid in the liver went up to 39.93g% on the 10th postoperative day, and the histological findings of the liver cells, stained by the method of Sudan III, revealed that the cells had been destroyed beyond recognition, with their nuclei missing, by the fat filling up the cells and the vacuoles formed — a finding of "totale Verfettung" (Fig. 6)

In other words, administration of methionine and vitamin B_{12} could not prevent the occurrence of fatty liver, so long as the amount of insulin given at the same time was small. It seems that the cases of this group developed a rather higher degree of fatty liver than those of group II. Compared with groups I and II, the cases of group III were found good in respect of appetite and general condition.

Table 4: Changes in the total amount of fatty acid in cases of group IV in which large amounts of insulin was given. (g%)

	Before Operation	After Operation			
		3th day	7th day	10th day	14th day
No.27	2.88	3.42		3.88	
No.31	2.09	2.97	6.70	9.97	
No.63	2.45	2.81		2.42	
No.25	2.86		2.98		3.36
No.29	2.33		3.23		3.86
No.51	3.14		3.66		3.48
No.59	2.82		3.86		2.13



4) Group IV

To this group as much as 5 u. per kg body weight of insulin was injected daily. The amount was divided into two or three and each was given after diet. In order to prevent insulin shock, 200cc to 300cc per day of 5% glucose solution was administered to all the cases before the injection of insulin. The result was, (1) that except case No. 31, which developed a slight degree of fatty liver, the other cases showed no trace of fatty liver until after 2 weeks; (2) the total amount of fatty acid in their livers remained within a normal range; (Table 4) (3) from histological examinations, only few fat globules were found in the liver cells of some of them, and although the arrangement of the liver cells was in disorder, no fatty liver could be observed (Fig. 7 and 8). In spite of the glucose solution given before the injection of insulin, case No. 29 had an attack of general convulsion fit on the 9th postoperative day; and case No. 31 had the same on the 9th postoperative day, which seems to have been caused by insulin shock. It may be added that in case No. 31 fatty liver developed to a slight degree, as is shown in Table 4. Compared with those of groups I, II and III, the cases of group IV showed a far better appetite and a much slighter degree of weakness.

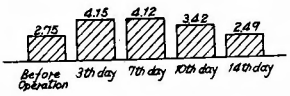
5) Group V

As had been expected, no fatty liver was observed and the histological findings were much the same as those of group IV (Table 5).

The above experiments have made it clear that fatty liver which develops soon

Table 5: Changes in the total amount of fatty acid in cases of group V in which were given both methionine, vitamin B_{12} and large amounts of insulin. (g%)

	Before Operation	After Operation 3th day	7th day	10th day	14th day
No.101	2.37		4.32		2.32
No.105	2.62		3.92		2.66
No.104	2.30	2.58		3.61	
No.106	3.62	5.72		3.23	



after total pancreatectomy, can be prevented by administration of large amounts of insulin, whereas methionine and vitamin B_{12} have no such action so long as the amount of insulin given at the same time is small. Thus the following experiments were carried on in order to determine the minimum amount of insulin necessary to prevent the occurrence of fatty liver.

Table: 6 Total amount of fatty acid in cases of group A in which 1 u. per kg body weight of insulin was given. (g%)

	Before Operation	After Operation 7th day	10th day	14th day	20th day
No. 85	2.61	7.32			
No. 83	3.13			10.66	
No. 81	3.00	8.42			
No. 79	2.82	6.34			2.04
No. 75	3.14	7.26	8.21		

A) Group A (Cases given 1 u. per kg body weight of insulin)

In all the 5 cases of this group was observed a slight degree of fatty liver with 6 to 10g% of fatty acid. One case, which was kept under observation for 20 days after the operation, was found at autopsy with no fatty liver, having only 2.04g% of the total amount of fatty acid. This figure means that the fatty liver had disappeared by the 20th postoperative day (Table 6).

Table: 7 Cases given insulin only after fatty liver occurred. (g%)

	Before Operation	On 3rd postoperative day	Amount of Insulin	Result
No. 15	1.77	7.36	per kg 2u.	1.93 17th day
No. 66	2.24	5.62	〃	3.40 10th day
No. 60	2.48	7.37	per kg 1u.	1.12 14th day

B) Group B (Cases given insulin only after fatty liver occurred.)

i) A case receiving no insulin was comfirmed to have a fatty liver developed on the 3rd postoperative day. By giving it 2 u. per kg body weight of insulin daily, however, the liver was restored to its previous state on the 7th postoperative day (Table 7).

ii) A case receiving no insulin was comfirmed to have a fatty liver developed on the 3rd postoperative day. By giving it 1 u. per kg body weight of insulin, however, the accumulation of fat disappeared on the 11th day of administration (Table 7).

These two cases show that fatty liver once developed can be cured by a daily administration of more than 1 u. per kg body weight of insulin.

C) Group C (Cases given a decreased amount of insulin)

Two cases receiving 3 u. per kg body weight of insulin daily were comfirmed 3

Table: 8 Cases given decreased amounts of insulin. (g%)

	Before Operation	After 3 Weeks	After decreasing
No. 11	2.65	5.32	12.77
No. 13	2.06	2.78	1.36

weeks after the operation to have no fatty liver developed. The amount of insulin given to them was then cut down to 1 u. per kg body weight. After a week, at autopsy, it was found that one of them developed a fatty liver with 12.77 g% of the total amount of fatty acid, while the other showed almost no fatty liver having 4.36g% of it, a slight increase over normal (Table 8).

In short, continuous administration of 1 u. per kg body weight of insulin made fatty liver once developed disappear, while a sudden decrease of the amount of insulin from 3 to 1 u. per kg body weight caused it to develop in one of the two cases.

INFLUENCE OF THE AMOUNT OF INSULIN UPON BLOOD-SUGAR AND SERUM LIPIDS

1) Changes in the blood-sugar level

The blood-sugar level began to rise immediately after the operation and reached a level nearly as high as 200mg% in 2 hours. Naturally, administration of a large amount of insulin can set the blood-sugar at a slightly lower level than when a smaller amount is given. However, the difference is not great, as is shown in Figure 1 and 2. With a large amount of insulin given, the value remained at such

Figure 1: Changes in the blood-sugar level after total pancreatectomy. (average)

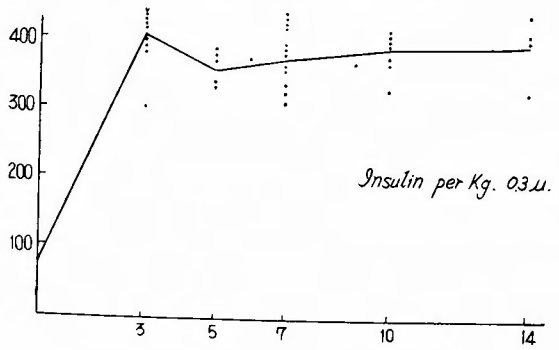


Figure 2: 5 u. per kg body weight of insulin. (average)

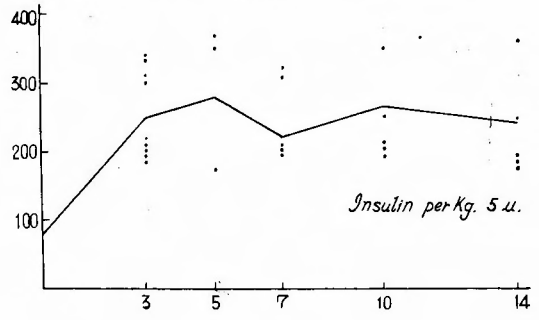
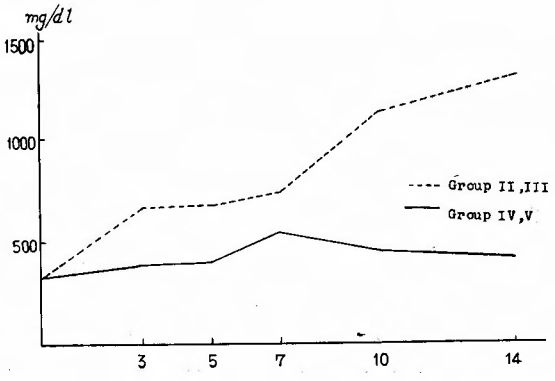


Figure: 3 Changes in the total amount of fatty acid in serum. (average)



considerably high levels as 200mg% to 250mg% through the course of observation. Even with a small amount of insulin given, the level did not go up so high, but remained within a range of 300mg% to 400mg%.

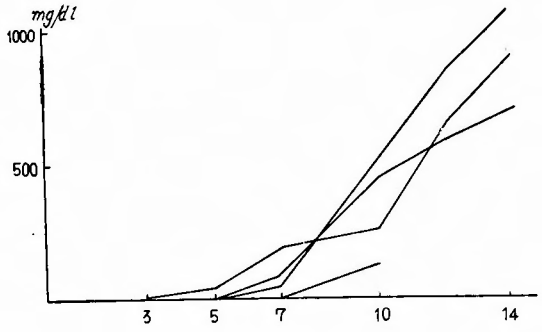
2) Changes in the total amount of fatty acid in serum

The method of VAN de KAMER was used and the mesurement was performed on the serum taken before removing a piece of the liver tissue. All the cases given a small amount of insulin showed a marked increase in the amount of fatty acid in serum (Fig. 3). The more the fat was accumulated in the liver, the more the amount increased, and many showed over 1000 mg/dl, and some rose as high as 2000 mg/dl. This hyperlipemia may have been caused by depot fat being brought to the liver in order to be changed into glycogen, making up for the release of liver glycogen caused by diabetes, or to form ketone bodies. Administration of a large amount of insulin could prevent hyperlipemia completely.

3) Changes in the value of ketone bodies in blood

The total ketone bodies were measured by the method of DUMM-SHIPLEY. Cases given a small amount of insulin showed a sudden increase in the amount of ketone bodies about 5 days after the operation, although the fatty acid rose immediately after the operation (Fig. 4). Cases given a large amount of insulin did not develop ketosis.

Figure 4: Changes in total ketone bodies. (Administration of small amount of insulin)



DISCUSSION

In order to observe the early development of fatty liver, I have performed the above experiments on totally pancreatectomized dogs, treated with different amounts of insulin. The results were: (1) all the cases given no insulin developed fatty liver, as AOKI in our clinic reported already; (2) such a small amount of insulin as 0.3 u. per kg body weight per day did not prevent the occurrence of fatty liver in all cases; (3) methionine and vitamin B_{12}, "lipotropic substances," failed to prevent the development of fatty liver, whereas large amounts of 5 u. per kg body weight of insulin completely checked the development of fatty liver up until 2 weeks after the operation. DRAGSTEDT stated that the fatty liver developed soon after total pancreatectomy might be diabetic in nature, and daily administration of insulin could remove the accumulation of fat in 2 weeks or so. My present experiments have also made it clear that this type of fatty liver is diabetic, caused by lack of insulin, and that a large amount of insulin can check its occurrence after the operation. It has also been comfirmed that, contrary to the opinions of some investigators, methionine and vitamin B_{12} are not effective at all in checking the occurrence of fatty liver.

It is well known that in order to prevent the fatty liver caused by total pancreatectomy, as a rule, far less amount of insulin is necessary than to check internal medical diabetes. However, with too little insulin, there is a danger of the occurrence of fatty liver. Then what is the minimum amount of insulin necessary to prevent the development of fatty liver? The question is, of course, hard to answer properly, but we have seen in the above experiments that continuous administration of as little as 1 u. per kg body weight of insulin caused the fatty liver once developed to disappear after 2 weeks, while a decrease in the amount of insulin from 3 to 1 u. per kg body weight developed a fatty liver. Moreover, in the report of his experiments on the later type of fatty liver, YAMAMOTO in our clinic said that by decreasing the amount of insulin down to 1 u. per kg body weight, he found to have fatty liver developed in two cases out of four. Taking these into consideration, I have come to the conclusion that more than 1 u. per kg body weight of insulin at least

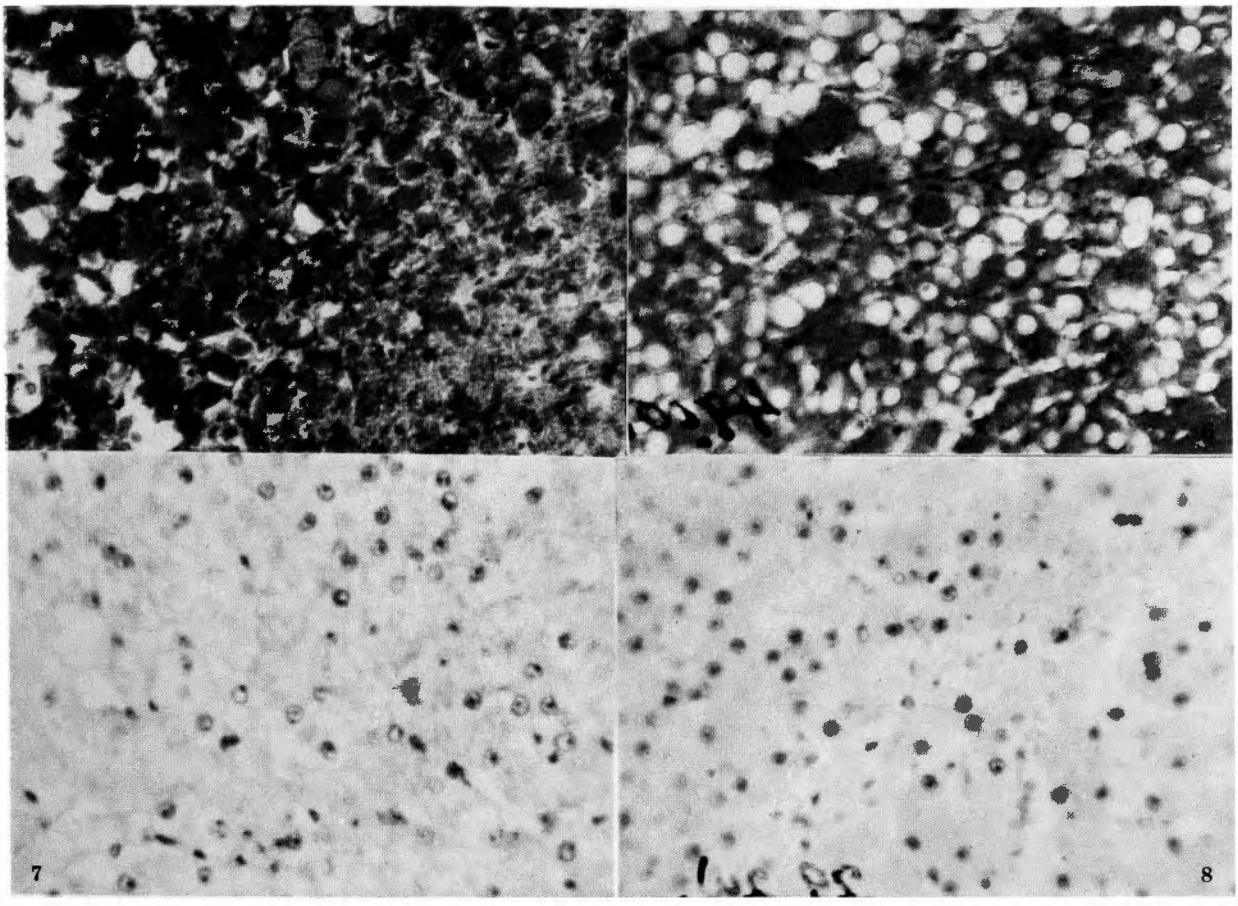


Figure. 5 No. 37, on 7th postoperative day. (Group Ⅱ)

Figure. 6 No. 49, on 10th postoperative day. (Group Ⅲ)

Figure. 7 No. 27, on 7th postoperative day. (Group Ⅳ)

Figure. 8 No. 29, on 14th postoperative day. (Group Ⅳ)

is the minimum necessary to check the occurrence of fatty liver. But is it not a contradiction that the same 1 u. per kg body weight of insulin caused a fatty liver, on the one hand, to occur and, on the other, to disappear? It is my belief that a sudden decrease, or lack of insulin in the body brings about a sudden unbalance of carbohydrate metabolism, which in its turn causes the development of fatty liver. On the other hand, administration of even a small amount of insulin, only if it is not suddenly decreased, makes it possible for anti-insulin hormones to lower their activities gradually, so that in the course of time the balance between insulin and anti-insulin hormones, which was once lost, are regained and settled at a lower level, and that makes the fatty liver once developed disappear gradually. This will explain the case in which case No. 47 once developed a high degree of fatty liver, but convalesced 2 weeks later. CHAIKOFF stated that the dogs which had been made to live for a considerably long period of time after the operation by continuous administration of insulin, came to develop a surprisingly high degree of fatty liver — over 40g % — when the insulin and diet had been cut off. From this fact it may easily be understood how rapidly the process goes on, from the unbalance of carbohydrate metabolism to the occurrence of fatty liver, through hyperglycaemia, the release of liver glycogen, and the moving of depot fat to the liver in order to make up for the release. The histological findings of the early type of fatty liver (accumulation of fat, but not fatty degeneration), do not contradict the results of my experiments that small changes in the amount of insulin could easily cause a fatty liver to develop or to disappear in a short period of time. It may be added that a supply of glucose solution together with administration of a large amount of insulin worked effectively in preventing the development of fatty liver.

What is the cause of fatty liver? It may be explained this way; in order to excite the lowered activity of carbohydrate metabolism in peripheral tissues, caused by lack of insulin, glycogen runs out of the liver into the blood stream, causing hyperglycaemia, so that depot fat has to be brought into the liver to be made into glycogen there, only to make it fatty. The results of experiments by YAO in our clinic showed that there is left little or no glycogen in the liver of totally depancreatized dogs, if given no insulin or only a small amount of it. This endorses the above opinion of mine. Thus it may not be denied that the supply of glucose solution worked effectively in preventing glycogen from running out of the liver, on the one hand, and from coming into it, on the other.

CONCLUSION

The present experiments have been made on totally depancreatized dogs treated with different amounts of insulin in order to observe the early development of fatty liver. The conclusions I have come to are as follows:

(1) The fatty liver developed soon after total pancreatectomy is diabetic in origin, caused by lack of insulin. It cannot be prevented by a small amount (0.3 u. per kg body weight) of insulin.

(2) Administration of 5 u. per kg body weight of insulin prevents the

occurrence of fatty liver.

(3) Methionine and vitamin B_{12} given together with insulin are not effective at all in checking the early development of fatty liver, if the amount of insulin is small.

(4) Administration of a large amount of insulin can completely prevent hyperlipemia and ketosis after total pancreatectomy.

(5) Once fatty liver develops, continuous administration of even 1 u. per kg body weight of insulin gradually restores the liver to its previous state. On the contrary, a sudden decrease of insulin from 3 to 1 u. per kg body weight causes fatty liver.

6) At least over 1 u. per kg body weight of insulin is necersasy to prevent the occurrence of fatty liver.

In closing, I wish to thank Prof. Dr. CHISATO ARAKI and Assist Prof. Dr. ICHIO HONJO for their guidance throughout the period of this work.

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和文抄録

膵臓全剔後の早期脂肪肝

(特にインシュリン投与量に就いて)

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膵臓全剔後の脂肪肝は，術直後より発生する早期脂肪肝と，術後6乃至8週頃より発生する後期脂肪肝とがあるが，私は早期脂肪肝の発生に関して，インシュリンの投与量及びメチオニン，ビタミン B_{12} の演ずる役割を検討するため，犬を用い，次の実験を行なつた．即ち，膵臓全剔犬を5群に分け，脂肪肝発生の有無，血糖値及び血中脂質の変動を観察した．

1. インシュリン無投与群
2. インシュリン少量投与群
3. インシュリン少量及び
   メチオニン，ビタミン B_{12} 投与群
4. インシュリン大量投与群
5. インシュリン大量及び
   メチオニン，ビタミン B_{12} 投与群

以上の結果1.2.3群では全例に高度の脂肪肝が発生し，4.5群では脂肪肝の発生はなかつた．同様に脂肪肝発生群では高脂血症，ケトージスを伴い，4.5群では全く認めなかつた．更にインシュリンの投与量を変えて飼育し，又，インシュリン減量等を行なつた結果次の結論を得た．

1) 膵臓全剔後の早期脂肪肝は，インシュリン不足に由来する糖尿病性脂肪肝で，インシュリン無投与の場合は勿論，1日体重kg当り，0.3単位のインシュリンでは発生を防止し得ない．

2) 1日体重kg当り5単位のインシュリン投与では全く発生を認めない．

3) メチオニン，ビタミン B_{12} 投与は早期脂肪肝には効がない．

4) インシュリンの大量投与により，術後の高脂血症及びケトージスを完全に防止し得る．

5) 体重kg当り1単位のインシュリン投与でも軽度の脂肪肝が発生するが，その持続投与により間もなく消失する．一方，体重kg当り3単位のインシュリン投与で脂肪肝の発生なきものでも，1単位への急激な減量で脂肪肝の発生を認めた．

6) 早期脂肪肝を防止するには，少くとも1日体重kg当り1単位以上のインシュリン投与が必要と思われる．